ISSN: 0975-766X
CODEN: IJPTFI
Available Online through *Research Article*
www.ijptonline.com

FORMULATION AND INVITRO EVALUATION OF BI-LAYERED MATRIX TABLETS OF GLIMEPIRIDE AND PIOGLITAZONE

K.L.Deepthi*[1], B.S.Raja[1], G.Vineetha, M.Sailakshmi, P.Sahitya, P.Preethi
Sri Venkateswara College of Pharmacy, Srikakulam, Andhra Pradesh-532001.
Email: deepthi.mpharmacy@gmail.com

Received on: 05-10-2018 *Accepted on: 18-11-2018*

Abstract:

The aim of the present study was to formulate and evaluate a bi-layer matrix tablet containing Pioglitazone as immediate release and Glimepiride as sustained release. Despite many advances in the development of oral hypoglycemic agents, an ideal drug for treating Type 2 diabetes is still a distant reality. The age-old molecules such as Biguanides which are still the drug of choice because of their pharmcodynamic profile, safety, tolerability. Formulation I C showed drug release for pioglitazone layer faster release which containing 1% Crosscarmellose sodium and 4% sodium starch glycolate used in the allowable range and for Glimepiride layer showed maximum delayed release which containing 2% Ethyl cellulose and 4% HPMC. The blend of different formulation were evaluated for Bulk density and Tapped density, Compressibility index, Angle of repose, Hausner's Ratio. The bi-layer matrix tablets for then evaluated for various physical tests like Uniformity of weight, Thickness test, Hardness test, Friability test, Disintegration time, Drug content analysis .

Keywords: Pioglitazone, immediate release, extended release, bi-layered, matrix tablet.

Introduction

Bilayered Tablets [1]:

The term bilayered tablets refers to tablet containing subunits that may be either the same (homogeneous) or different (heterogeneous). Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, either as second dose or in an extended release manner [11]. Bilayer tablet is suitable for sequential release of two drugs

in combination, separate two incompatible substances. Bilayer tablets are preferred when the release profiles of the drugs are different from one another. In this study we had made an attempt to develop an advanced drug delivery of oral hypoglycemic agents, particularly the development of sustained release dosage form Pioglitazone and Glimepiride combination, both of which have great promise in treatment of Type 2 diabetes mellitus. The type of combinations will give better compliance and a relative freedom from mealtime drug administration, thus, improving the quality of life. More importantly, because of prolonged duration of action it shall produce a strict round the clock control of blood glucose without producing severe hypoglycemia. For better beneficial action, Pioglitazone requires administration of 15 mg twice daily whereas Glimepiride which increases insulin secretion requires 4-8 mg once daily. Therefore, the dose can be reduced by formulating both Pioglitazone and Glimepiride as sustained release bilayer matrix tablet for once daily administration.

Methods:

Formulation of Bilayer Matrix Tablet:

The Bilayer tablet was prepared by direct compression method. Development of Bilayer tablet of pioglitazone nd Glimipride was carried out in three stages. Two layers (Immediate release layer and controlled release layer) were formulated seperatey using different concentrations of polymers in different ratios. After optimization of individual layers by in-vitro studies and statistical methods Bilayer tablet was prepared using optimized formulae [12]. Bilayer tablet was prepared on rotary tablet compression machine. Composition of immediate release and extended release layers are shown in Tables 1 and 2

Table-1: Composition of immediate release layer.

Formulationcode composition (mg)	**I_1**	**I_2**	**I_3**
Pioglitazone	1.5	1.5	1.5
Caroscarmellose sodium	0.25	0.5	0.75
Sodium starch glycolate	2.25	2	1.75
Microcrystalline cellulose	3.0	3.0	3.0

Talc	2	2	2
Magnesium stearate	0.5	0.5	0.5

Table-2: Composition of extended release layer:

Formulation code composition	**C_1**	**C_2**	**C_3**	**C_4**	**C_5**
Glimepiride	2	2	2	2	2
Ethylcellulose	5	10	15	20	25
HPMC K4M	25	20	15	10	5
Microcrystalline cellulose	15.5	15.5	15.5	15.5	15.5
Talc	2	2	2	2	2
Magnesium stearate	0.5	0.5	0.5	0.5	0.5

Angle of repose [2]:

The angle of repose is defined as the maximum angle possible between the surface of a pile powder and the horizontal plane. Funnel method was used to measure the angle of repose of blends. A funnel was fixed with its tip at given height 'h' , above a flat horizontal surface to which a graph paper was placed . powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel .the angle of repose was then calculated using following equation : $\tan \theta = h/r$ where θ = angle of repose , h = height of pile ,r = radius of the base of the pile.

Bulk Density and Tapped Density [2]:

2 gm of powder from each blend were taken into a 10 ml measuring cylinder. After the initial volume was observed, the equipment was on and the cylinder was allowed to fall under its own weight into a hard surface. The reading of tapping was continued until no further change in volume was noted. Using the following equation Bulk Density and Tapped Density was calculated.

Tapped density(g/ml)= mass of the powder / tapped volume

Compressibility index and Hausner's ration [13]:

Compressibility index = (Tapped density – Bulk Density X 100) / Tapped density [9]

Hausner ration is the measurement of frictional resistance of the drug and the ideal range should be 1.2 – 1.5.

Hausner Ratio = Tapped Density /Bulk Density X 100

Uniformity of weight [3,14]:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation, if not more than two of the individual weight deviates from the average weight by more than the percentage limit. IP limit for weight variation in case of tablets weighing up to 80 mg or less is ± 10% , 80 to 250 mg is ± 7.5 %, and more than 250 mg is ± 5%.

Thickness [8] :

The control of physical dimension of the tablet such as essential for consumer acceptance and to maintain uniformity of tablet weight. Six tablets were randomly selected from each batch and their thickness was measured by using verniercallipers. The average thickness and diameter with standard deviation of the tablets from each batch ewre calculated and tabulated.

Hardness [2] :

The tablet crushing load is the force required to break a tablet by compression. Hardness was measured by using hardness tester (Pfozer hardness tester). For each batch, six tablets were selected randomly and evaluated. Hardness of about 4-6 kg/cm^2 is considered to be minimum for uncoated tablets and for mechanical stability.

Friability [3]:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for this purpose. Pre weighed sample of twenty tablets were placed in the friabilator, which was then operated for 100 revolutions the tablets were dusted and re weighed. Compressed tablets should not lose more than 1% of their weight.

Percentage Friability = Initial Weight / Final weight X 100

Disintegration [2]:

Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in simulated gastric fluid (37 ± 0.5^{0}C) using United States Pharmacopeia (USP) disintegration apparatus. The mean ± standard deviation (SD) of six tablets were calculated.

Drug Content Analysis [4,15] :

Drug content for Glimepiride:

Twenty tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 2 mg of Glimepiride taken 100ml volumetric flask. The amount of drug present in a 2 mg equivalent amount of powder was determined by, dissolving the powder mixture n HClbuffer P^H 2.0 containing 0.5 % w/v of SLS and suitably diluted. Further 1 ml of the above solution was diluted to 10 ml with HCl buffer P^H 2.0 containing 0.5 % w/v of SLS [7]. Drug concentration was determined from simultaneous equation and results are shown in table no 4

Drug content for Pioglitazone [16]:

Twenty tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 15mg of Pioglitazone was taken into 100 ml volumetric flask. The amount of drug present in a 15 mg equivalent amount of powder dissolved in and diluted with HCl buffer P^H 2.0 containing 0.5 % w/v of SLS. Further 1 ml of the above solution was diluted to 10 ml with HCl buffer P^H 2.0 containing 0.5 % w/v of SLS. Drug concentration was determined from Simultaneous equation and results are shown in table no 4.

Procedure:

In vitro drug release studies [5] :

The release of drug from different batches of prepared tablets was studied by using USP dissolution apparatus type II (paddle type). The dissolution medium used was 900 ml of HCl buffer of P^H 2.0 for 2 hr and phosphate buffer of P^H 6.8 for 10hr. The temperature was maintained at 37 ^{0}C ± 0.5 ^{0}C with continuous stirring at a rate of 50 rpm. Sample were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV Spectrophotometer at 279nm for immediate release layer Pioglitazone and Glimepiride at 238nm for sustain release layer against a blanks.[6]

Results & Discussion:

Invitro evaluation of immediate release tablets:

The in-vitro study was carried out by using USP dissolution apparatus II (paddle type) and results were shown in the Table no. From the dissolution profile of all the extended release formulations i.e (C_1 –C_5). It was found that the formulation C_2, C_3, C_5 showed drug release up to 12 hr. In these three formulations C_2 showed best release profile

when compared to the other two formulations. The formulation C_1 and C_4 showed their release profile up to 11 hr only. It is because of the presence of more amount of hydrophilic matrix in C_1 formulation. Faster release of drug from the hydrophilic matrix was probably due to gel effect, erosion effect. C_4 formulation released drug up to 11 hr higher release rate because of friction of ethyl cellulose is in comparison to HPMC. Formulation C_2 containing Ethyl cellulose (2%) and HPMC (4%) showed maximum delayed release. Possibly swelled gel of HPMC might have packed sufficiently the aforementioned cracks. The drug release of C_2 formulation in 2 and 12 hr was 19.36% and 84.26% respectively. From the dissolution profile of all immediate release formulations i.e (I_1-I_3), it was found that I_2 formulation showed faster release. It has 1% Cross carmellose sodium and 4% sodium starch glycolate used in the allowable range. The drug released was 89.52% within 60 min. I_1 formulation showed 85.31% drug release within 60 min because of presence of less percentage of cross carmellose sodium. I_3 formulation showed 81.91 % drug release within 60 min because of excess super disintegrants. Comparative in-vitro drug release pattern of immediate release layers of Pioglitazone was shown in Fig 15. The extended release formulation C_2 and immediate release formulation I_2 showed best release. Hence I had chosen I_2C_2 as the optimized formulation for further studies.

Table-3:- Physico-chemical characteristics of bilayer matrix tablets.

Formulation Batch Code	**Average Weight(G)**	**Hardeness (Kg/Cm^2)**	**Thickness**	**Friability**	**Disintegration time (Sec)**
I_1C_1	101.4	3.78	2.75	0.58	36
I_1C_2	101.4	4.28	2.84	0.69	36
I_1C_3	101.7	4.23	2.49	0.62	36
I_1C_4	101.9	5.17	2.72	0.54	36
I_1C_5	101.5	3.82	2.61	0.4	36
I_2C_2	101	5.13	2.52	0.58	30
I_3C_2	101.7	5.17	2.5	0.47	75

Table-4: Drug content analysis of bilayer matrix tablets.

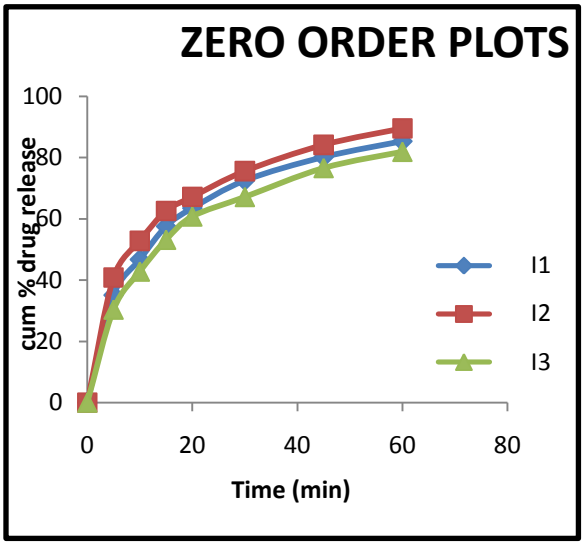
Formulation batch code	**Drug content in P^H 2.0 HCl buffer ±S.D**		**Drug content in P^H 6.8 phosphate buffer ±S.D**
	PIOGLITAZONE	GLIMEPIRIDE	
I_1C_1	93.20	92.13	93.10
I_1C_2	95.38	96.48	96.60
I_1C_3	91.16	95.22	94.93
I_1C_4	93.68	92.65	95.54
I_1C_5	92.98	93.11	92.18
I_2C_2	95.89	95.86	96.29
I_3C_2	93.31	94.85	94.40

Table 5:- Pre compression parameters of immediate release layer:

Formulation Batch code	**Angle of repose**	**Bulk density (g/ml)**	**Tapped Density (gm/ml)**	**Carr's index**	**Hausner's ratio**
I_1	27.95	0.454	0.498	8.84	1.10
I_2	27.91	0.468	0.521	10.17	1.11
I_3	28.64	0.491	0.545	9.91	1.11

Table-6: Precompression parameters of extended release layer:

Formulation Batch code	**Angle of repose**	**Bulk density (gm/ml)**	**Tapped density (g/ml)**	**Carr's index (%)**	**hausner's ratio**
C_1	28.13	0.465	0.518	10.23	1.11
C_2	28.33	0.545	0.597	8.71	1.10
C_3	29.18	0.606	0.665	8.87	1.10
C_4	27.97	0.594	0.673	11.74	1.13
C_5	28.53	0.486	0541	10.97	1.11



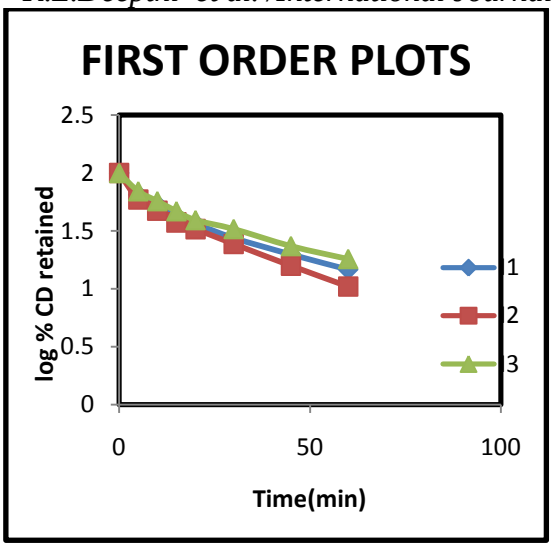
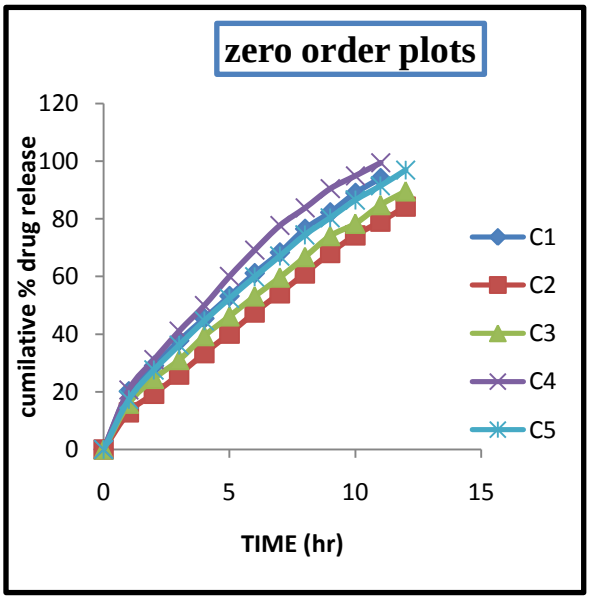


fig.no:1 **fig.no.:2**

Fig.no:1- comparative zero order plots of immediate release layers of pioglytazone.

Fig no:2- comparative first order plots of immediate release layers of pioglytazone.



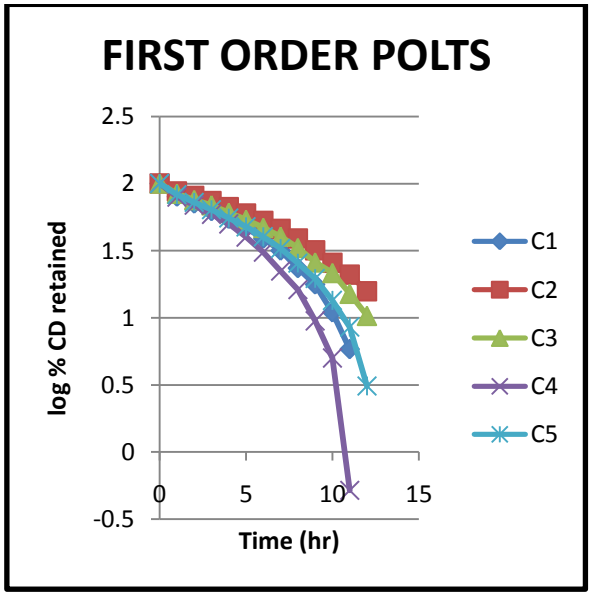


fig.no:3 **fig.no:4**

Fig 3 :-comparative zero order plots of extended release layers of glimepiride

Fig 4 :- comparative first order plots of extended release layers of glimepiride

Conclusion:

Formulation I C showed drug release for pioglitazone layer faster release which containing 1% Croscarmellose sodium and 4% sodium starch glycolate used in the allowable range and for Glimepiride layer showed maximum delayed

release which containing 2% Ethyl cellulose and 4% HPMC.Curve fitting analysis showed the drug release data of extended release layer fitted well in to Zero Order Kinetics and drug release data of immediate release fitted well into first order kinetics. Optimized formulation I C compared with conventional marketed product in in-vitro dissolution and concluded that I C showed faster release in case of Pioglitazone layer and showed more extended release n case of Glimepiride layer.

Conflicts of Interest: NONE.

References:

1. Patel M , Sockan Gn , Kavitha , Tamizh M . Challenges In The Formulation Of Bilayered Tablets : A Review International Jounal Of Pharma Research And Development , 2010; 2(10) : 30-42 .
2. Bhavesh S , Surendra G , Sanjay S . Formulation and Evolution Oif Bilayered Tablet Of Metaclopramide Hydrochloride And Ibuprofen. AAPS Pharma Sci Tech, 2008 ; 9 (3) : 818-827 .
3. Hosna B , Mostafa Reaj S , Muhammad Shahdaat Bs , Irin D , Ashraful Islam Sm , Formulation Development Of Bilayer Acetaminophen Tablets For Extended Drug Release . J Chem Pharm Res.2011,3(6) : 348-360.
4. Indhumathi D, Grace R . Design And Optimization Of Orodissolving Tablets Of Antidepressant Drug By Super Disintegrents Additipon Method. Ijpsrr . 2010; 2(2): 1-9.
5. Sharma S , Sharma A, Jha Kk. The Study Of Captopril Floating Matrix Tablets Using Different Polymers As Release Retariding Agent . T Ph Res . 2009;1:34-40.
6. Catherine C. C. Diabetes-vital statistics. USA: American Diabetes Association ; 1996. P. 65-8.
7. Harris MI, Diabetes in America, National Institute of Diabetes, and Digestive and kidney disease . 2nd ed. NIH publications, 1995; 95: 1468.
8. Consensus Statement (ADA), Diab care. 1995; 18 : 1510-8.
9. Helping the pancreas produce insulin. [online].2007 sep 21 cited 2011 Dec 10 available from http://www.healthvalue.net/diabetespancreasbeta.html.
10. Kadhe G, Arasan RE. advances in drug delivery of oral hypoglycemic agents . current science, 2002 Dec ; 83(12):1539-43.
11. Anisul Q, Karl Ka. Comparative Study of Current Super Disintegrates. Pharmaceutical Technology. 2006 Oct 1.

12. Chein Yw.Novel Drug Delivery System. New York : Marcel Dekker .Inc ; 1982: 465- 574.
13. Kibbe Ha. Hand Book of Pharmaceutical Excipients. 3rd Ed. London: American Pharmaceutical Association, Pharmceutical Press; 2000.
14. Ammar H.O, Salama H.A, Ghorab M, Mahmoud A A . Formulation And Biological Evalutions Of Glimepiride-Cyclodextrin- Polymer Systems . Int J Pharm. 2006;309:129-138.
15. Rubina Reichal C, Bhagya Lakshmi J,Ravi Tk . Studies On Formulation And Invitro Evalution Of Glimepiride Floating Tablets . J Chem Pharm Res. 2011; 3(3) : 159-64.
16. Rajendran Nn, Natarajan R,Patel H. Formulation And Evalution Of Sustained Release Bilayer Tablets Of Metformin Hcl And Pioglitazone Hcl . Int J Cur Pharm Res. 2011;3(3): 118-22.
17. Santanu G , Barik Bb. Preparation And Evalution Of Aceclofenac Sustained Release Formulation And Comparision Of Formulated And Marketed Product . International Journal of Medicine and Medical Sciences. 2009;1(9):375-82.
18. Papoushek C. The "Glitazonas " : Rosiglitazone And Pioglitazone . J Obstet Gyneacol . 2003;25:812-15.

Corresponding Author:

K.L.Deepthi*,

Email: deepthi.mpharmacy@gmail.com